REMARKS

In the interest of simplifying the pending claims set, Applicants have canceled claims 1-49, and added new claims 50-66. Support for these claims can be found throughout the specification as filed, including the claims. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have withdrawn newly added claims 60-66, as drawn to unelected Group II method claims. However, upon allowance of the elected composition claims, Applicants request rejoinder of the withdrawn method claims.

Applicants note that new claims 54 and 59 recite that the claimed compositions further comprise zonisamide or a pharmaceutically acceptable salt thereof. In the previous Office Action dated April 5, 2007, the Examiner stated that newly added claims reciting zonisamide as a third component were directed to an invention that is independent or distinct from the originally elected invention, and would therefore be withdrawn from further consideration. Applicants respectfully submit that new claims 54 and 59 should be considered as proper species claims that are dependent from the elected broader generic claims 50 and 55, respectively. As stated in 37 C.F.R. § 1.141

> Two or more independent and distinct inventions may not be claimed in one national application, except that more than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in one national application, provided the application also includes an allowable claim generic to all the claimed species and all the claims to species in excess of one are written in dependent form (§ 1.75) or otherwise include all the limitations of the generic claim. *37 C.F.R. § 1.141* (emphasis added).

Thus, Applicants understand that according to Rule 1.141, the Examiner should examine claims 50 and 55, and determine if Applicants are entitled to generic claims 50 and 55. If the generic claims 50 and 55 are allowed, then dependent claims 54 and 59 to species of generic claims 50 and 55 should be examined and allowed as well.

For the reasons discussed below, Applicants respectfully traverse the pending rejections of the Office Action mailed June 11, 2007.

35 U.S.C. § 112, First Paragraph – Written Description

The Examiner has rejected claims 8, 36 and 48-49 as lacking adequate written description based on the recitation of "prodrug thereof." Solely in the interest of furthering prosecution, Applicants have canceled claims 8, 36 and 48-49, and the pending claims do not recite "prodrug thereof," rendering this rejection moot.

35 U.S.C. § 112, Second Paragraph – Indefiniteness

The Examiner has rejected claims 8 and 36 as indefinite based on the recitation of "compound comprises." Solely in the interest of furthering prosecution, Applicants have canceled claims 8 and 36, and the pending claims do not recite "compound comprises," rendering this rejection moot.

35 U.S.C. § 102(b) – Anticipation

The Examiner has rejected claims 8-9, 36-43 and 48-49 under 35 U.S.C. § 102(b) as being anticipated by O'Malley et al. (US Patent 6004970). The Examiner states that O'Malley "discloses a composition comprising an opioid antagonist (i.e., naltrexone) in combination with nicotine and antidepressant (i.e., bupropion hydrochloride) ... wherein said composition is prepared and administered in various dosage forms including sustained release preparation, oral, intravenous, intramuscular or intradermal, e.g., by sterile injections, including depot versions...." *Office Action* at 5. The Examiner further states that with respect to recitation of "a sustained release formulation, "O'Malley's composition comprising naltrexone and bupropion in depot versions or implants 'metes and bounds' the claimed invention." *Office Action* at 6. Applicants respectfully traverse.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). However, where a reference does not specifically disclose the claimed composition, but instead discloses various disparate elements of the claimed composition, the claimed composition is not anticipated: "To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim," *Brown v. 3M*, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001)

(emphasis added); "every element of the claimed invention must be identically shown in a single reference. These elements must be arranged as in the claim under review," *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990) (citations omitted, emphasis added); *see also M.P.E.P. §2131.*

New claim 50 recites a composition comprising "a weight loss affecting amount of the combination of: (a) naltrexone or a pharmaceutically acceptable salt thereof; and (b) a sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof; wherein said composition is formulated for oral administration." Similarly, claim 55 recites a pharmaceutical composition comprising "a weight loss affecting amount of the combination of: (a) naltrexone or a pharmaceutically acceptable salt thereof; and (b) a sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient, diluent, or carrier, wherein said composition is formulated for oral administration." Applicants submit that O'Malley does not disclose the recited combination of naltrexone and a sustained release formulation of bupropion (or their pharmaceutically acceptable salts) in a formulation for oral administration.

The Examiner cites several portions of O'Malley to support his rejection, picking and choosing from disparate laundry lists in order to purportedly assemble the claimed invention. However, O'Malley does not expressly or inherently disclose each and every claim element, and nowhere does O'Malley disclose the elements of the pending claims arranged in a composition combining naltrexone and a sustained release formulation of bupropion (or their pharmaceutically acceptable salts) in a formulation for oral administration.

O'Malley does not expressly disclose a composition combining naltrexone and a sustained release formulation of bupropion. General disclosures of embodiments wherein "an opioid antagonist is administered in conjunction with an effective amount of an antidepressant or other agent known by the skilled worker to treat withdrawal, especially the depression associated with smoking cessation (such as Welbutrin®, Paxil®, Sertraline®, Buspar®, Zofran® or Prosac®)," are not a disclosure of elements arranged in a composition comprising the combination of naltrexone and sustained release bupropion. *O'Malley* at col. 6, lines 1-6.

Applicants note that claim 1 of O'Malley recites "A method for treating a person for nicotine dependency comprising administration to the person of (a) an effective amount of

naltrexone, and (b) an effective amount of nicotine," while claim 16 recites "A method according to claim 1 further comprising administering bupropion hydrochloride to the person." This method is not an express or inherent disclosure of a composition comprising naltrexone and a sustained release formulation of bupropion (or their pharmaceutically acceptable salts) in a formulation for oral administration since it is a method claim, not a composition claim. Clearly, these claims do not require the administration of a composition that comprises a combination of the recited components, since the method can use different routes of administration for each of the compounds. For example claim 10 recites that the nicotine of claim 1 can be delivered by inhaler, while claim 11 recites that the naltrexone of claim 1 can be administered by intravenous injection. Clearly, the method of claim 1 does not inherently require the administration of the recited compounds in a composition – the same is true of dependent claim 13.

Nor does O'Malley expressly disclose a sustained release formulation for oral administration. Reference to "sustained release preparations" generally in O'Malley is not sufficient to anticipate the pending claims wherein the claimed composition of naltrexone and a sustained release formulation of bupropion is for oral administration, since "sustained release preparations" are not inherently formulations for oral administration. This is apparent from claims 13 and 14 of O'Malley. Claim 13 recites "wherein the opioid antagonist is administered in a sustained release preparation." Claim 14 recites "A method according to claim 13 wherein naltrexone is administered using a transdermal patch." Clearly, a "sustained release preparation" is not inherently for oral administration, and thus this general disclosure of "sustained release preparations" does not anticipate the pending claims.

In sum, O'Malley does not expressly or inherently disclose each and every element of a composition comprising naltrexone and a sustained release formulation of bupropion (or their pharmaceutically acceptable salts) in a formulation for oral administration. Nor does O'Malley disclose the elements arranged as in the pending claims. Therefore, Applicants respectfully submit that rejection of the pending claims under 35 U.S.C. § 102(b) as anticipated by O'Malley is improper, and request that the Examiner not issue such a rejection.

35 U.S.C. § 103(a) – Obviousness

Claims 8-9, 36-43 and 46-49 are rejected under 35 U.S.C. § 103(a) as being unpatentable over O'Malley "in view of applicant's admission of the prior art of record (para. [0100]), and further in view of Li (US 6589553) and Cook (US 6071918). *Office Action* at 8. The Examiner asserts that Applicant admits that various sustained-release materials have been established and are well known by those skilled in the art, and that Li and Cook demonstrate the routine knowledge in preparing naltrexone and bupropion in controlled or sustained release formulation. *Id.* The Examiner states that "[t]he teaching of O'Malley differs from the claimed invention in incorporating sustained release bupropion into said composition," and that "to incorporate such teaching into the teaching of O'Malley, would have been obvious" in view of Applicant's "admission" or the cited references. *Id.* Applicants respectfully traverse.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness, including showing that each and every element of the claimed invention is taught or suggested in the prior art, and that there is a reasonable likelihood of success. As noted above, O'Malley does not disclose each and every element of the claimed invention, and fails to disclose the elements arranged as claimed. The method of treating a person for nicotine dependency in O'Malley claims 1 and 16 discloses a method, not a composition; the method can be practiced by administration of naltrexone, nicotine and bupropion at different times or even different days (*e.g.*, *O'Malley* at claim 7 "another compound is administered to the person at any time before, after, or during the treatment" and *O'Malley* at Example 3); and the method can be practiced by any number of different routes of administration (*e.g.*, *O'Malley* at claim 11 "naltrexone is administered to a person using a method selected from the group consisting of oral administration, intravenous injection, intramuscular injection, intradermal injection, a depot version of intradermal administration, implants, parenteral administration, and combinations of these.") Only by impermissibly using hindsight would the Examiner elect to combine naltrexone and bupropion in a composition formulated for oral administration – this combination of elements is not taught by O'Malley.

Applicants have determined that the combination of naltrexone and sustained release bupropion as set forth in the present claims can provide unexpected synergistic weight loss. This synergism is likely dependent at least in part on the pharmacokinetics of the claimed

combination, something which is not taught in the cited art. Finally, Applicants disagree with the Examiner's characterization of para [0100] of the specification as an admission – it cannot reasonably be construed to state that the claimed combination was known in the art. For at least these reasons, a *prima facie* case of obviousness has not been established. Even if it were, however, that would not be determinative here, due to unexpected synergistic results of record.

Without conceding a *prima facie* case of obviousness, Applicants again direct the Examiner's attention to the previously submitted evidence that the claimed combinations of oral formulations of naltrexone and sustained release bupropion (buproprion SR) have unexpected properties, such that the claimed compositions are non-obvious. Applicants note that §2141 ¶ III of the M.P.E.P., titled "**Objective Evidence Must Be Considered,**" states that: "Objective evidence or secondary considerations such as unexpected results...are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence." *M.P.E.P. §2141 ¶ III* (emphasis added). Applicants respectfully request that the Examiner evaluate the question of obviousness in light of the previously submitted evidence of record.

Pursuant to 37 C.F.R. § 1.132, Applicants previously submitted in the response filed on January 23, 2007, as Exhibit 1, a declaration of Michael A. Cowley, Ph.D., an expert in the field and co-inventor of the instant application. As Dr. Cowley's declaration states, the combination of naltrexone and bupropion SR has unexpected, non-obvious properties.

In particular, Applicants have not merely submitted anecdotal evidence of a purported benefit. Instead, Dr. Cowley reports strongly synergistic results seen in well controlled, statistically-significant human clinical trials of the combination of naltrexone and bupropion SR to treat obesity. Dr. Cowley states, in part, that for the completer population of the Phase IIb trial, between 64-70% of patients administered the combination lost at least 5% of their body weight, compared to 32% for bupropion SR alone, 15% for naltrexone alone and 20% for placebo. *Cowley Declaration* at ¶5. Of patients receiving the combination, 24-32% of patients in the completer group lost at least 10% of their body weight, compared to 9% for bupropion SR alone, 3% for naltrexone alone and 3% for placebo. *Id.* These detailed clinical studies of record demonstrate that the claimed combination of naltrexone and bupropion SR can provide

synergistic effects which are unexpected in comparison to the results of the components when administered alone.

Because a composition and its properties are considered together in determining obviousness (*In re Papesch,* 315 F.2d 381, 137 USPQ 43 (CCPA 1963)), and because unexpected synergistic results are seen with the claimed combination of naltrexone and bupropion SR, any *prima facie* case of obviousness has been overcome. *See, e.g., M.P.E.P. §2144.09* (citing *Papesch*) and *M.P.E.P. §716.02 - §716.02(g).*

The Examiner states that "As discussed above, the applicant's statement of 'the affecting weight loss' is not limited to the interpretation of the composition claims since such property or characteristic deems to be expected feature of the referenced composition (due to overlapping dosage amounts)." *Office Action* at 9.

To the extent that the Examiner is arguing that the unexpected properties discussed above are not relevant because they are inherent in the cited references, Applicants note that M.P.E.P. §2112, part IV, states that the "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). As discussed above, O'Malley, alone or combined with the other cited references, does not disclose the claimed compositions. Therefore, the burden is on the Examiner to provide a rationale to support any assertion that the cited references necessarily possess the unexpected properties.

Given the numerous possible ways of combining the many compounds recited in O'Malley, the various routes of administration of the compounds at various times, and the lack of disclosure of bupropion SR, there is no reasonable basis to assume that the disclosures in O'Malley inherently possess the unexpected properties of the claimed compositions. "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *M.P.E.P. §2112, part IV* (emphasis in original). The Examiner appears to argue that if the combinations of compounds and methods disclosed in O'Malley were optimized they would inherently posses the properties of Applicants' claimed compositions. However, a mere possibility based on optimization is not sufficient to establish inherency. *See M.P.E.P. §2112, part IV, citing In re Rijckaert*, 9 F.3d 1531, 1534, 28

USPQ2d 1955, 1957 (Fed. Cir. 1993) ("reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art").

In light of the failure of the Examiner to establish a *prima facie* case of obviousness, and Applicants' evidence of unexpected results, Applicants respectfully submit that rejection of the pending claims under 35 U.S.C. § 103(a) as obvious over O'Malley in light of Li and Cook is improper, and request that the Examiner not issue such a rejection.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 6/28/07

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